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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/587,386	05/03/2007	Stefan Schorling	22398-US	4893

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Roche Molecular Systems, Inc.
4300 Hacienda Drive
Pleasanton, CA 94588

EXAMINER	
THOMAS, DAVID C	

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
12/23/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/587,386	SCHORLING, STEFAN	
	Examiner	Art Unit	
	DAVID C. THOMAS	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 October 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-10,15 and 16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-10,15 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed October 7, 2010 is acknowledged. Claim 4 (currently amended) and claims 5-10, 15 and 16 (original or previously amended) will be examined on the merits. Claims 1-3, 11-14 and 17-24 were previously canceled.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 4, 5 and 8-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schmidt et al. (Vox Sanguinis (2001) Vol.81, No.4, pp.228-235), in view of Hemauer et al. (J. General Virology (1996) Vol.77, pp.1781-1785) and further in view of Lowe et al. (Nucleic Acids Res. (1990), Vol. 18, No.7, pp. 1757-1761).

Regarding claims 4, 5, 8 and 10, Schmidt discusses a method comprising: (a) providing a sample suspected to contain the target nucleic acid, (b) providing a pair of primers comprising a first and a second primer, (c) amplifying the target nucleic acid, (d) contacting the sample with a probe under conditions for binding the probe to the target nucleic acid, and (e) detecting the binding product between the target nucleic acid and the probe as an indication of the presence of the target nucleic acid (see p. 229, "Quantitative TaqMan PCR" where Schmidt discusses the method including two primers

and a doubly labeled probe within the NS1 region. Schmidt states the primers and probes are within nucleotides 2030 to 2171 of the B19 Genome).

Regarding claim 9, Schmidt discusses the method wherein the target nucleic acid in step c) is amplified with a template-dependent DNA polymerase (see p. 229, "Quantitative TaqMan PCR" where Schmidt uses TaqGold Polymerase).

Schmidt does not discuss the method whereby the first primer has a nucleic acid sequence consisting of SEQ ID NO: 15, and whereby the second primer consists of SEQ ID NO: 17. Schmidt also does not discuss the method wherein the probe has the sequence consisting of SEQ ID NO: 11. However, Schmidt discusses primers and a probe that are nearby to such sequences as the instant SEQ ID NOs: 11, 15 and 17, located within the same NS1 region of the Parvovirus B19 genome.

Hemauer teaches the Parvovirus B19 DNA, genome position 1924-2317, identified as Genbank Accession Number Z70553. This sequence comprises SEQ ID NO: 11 (nucleotides 147-172), SEQ ID NO:15 (nucleotides 121-140) and SEQ I D NO: 17 (nucleotides 270-251). In Hemauer's research, he identifies this region (i.e. genome position 1924-2317) being within the NS1 coding region, and is more specifically included in the NS1-C region (see Figure 1). Hemauer also teaches nearby primers to amplify this region (see Table 2 on pg.1783).

One of ordinary skill in the art would have been motivated to modify the method of Schmidt to use primers of SEQ ID NO: 15 and 17 and a probe sequence of SEQ ID NO: 11 because Schmidt demonstrates the benefits of designing and using similar

primers and a probe targeting the NS1 region of the Parvovirus B19 genome, and Hemauer et al. shows that the Parvovirus B19 sequence comprising the primer sequences of SEQ ID NO: 15 and 17 and probe sequences of SEQ ID NO:11 was known in the art and also designed nearby primers that amplify this same region. Additionally, Hemauer also notes that amplification of the NSC-1 region was able to show positive PCR results in contrast to other regions of the Parvovirus B19 genome and also noted that there is a relatively conserved stretch of about 220 bp with only a few alterations in nucleotides 2020-2240 of this region (see pg.1783, right column). Therefore, since the sequences of primers SEQ ID NO: 15 and 17, and probe sequences of SEQ ID NO: 11 are located in this conserved stretch, one of skill would have recognized that amplification and detection of such a conserved region would allow for detection of multiple different parvovirus B19 sequences in a universal method. Therefore, the skilled artisan would have had a reasonable expectation of success in modifying the method of Schmidt to substitute for similar and equivalent primers and a probe derived from the same well-known and amplifiable conserved stretch of the NSC-1 region, resulting in the predictable amplification and detection of multiple different parvovirus sequence variants. It would have been obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the claimed primer and probe therein.

In the recent court decision *KSR International Co. v. Teleflex Inc., 82* 127 SCt 1727 (2007), the U.S. Supreme Court determined that if the combination of the claimed

elements was "obvious to try" by a person of ordinary skill, this might show that such a combination was obvious under §103. Regarding "obvious to try", the Court stated:

"A person of ordinary skill is also a person of ordinary creativity, not an automaton. The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was "obvious to try." Id., at 289 (internal quotation marks omitted). When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103."

Since the claimed primers and probe simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for detection of the NS1 region of the Parvovirus B19 genome and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

With regard to the issue of equivalence of a polynucleotide sequence, MPEP 2144.06 notes "Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

With regard to the issue of reasonable expectation of success in using such equivalents at the time the invention was made, as shown in Lowe, one of skill in the art was clearly aware of the factors involved in designing amplification primers from a known sequence, and would have routinely and predictably designed any such primers. Specifically, Lowe teaches a computer program based on a set of rules which take into account both the sequence of the primers and the amplified region of DNA, such that primer-to-target hybridization is enhanced, while facilitating attainment of full-length extension products by minimizing non-specific product formation and self-priming (see Abstract and p. 1757, column 2, line 33 to p. 1758, column 1, line 41). The program has been tested on a variety of gene products for RT-PCR, for both total and cytoplasmic RNA samples prepared by several different methods (Lowe, p. 1758, column 2, last 2 lines). "Experimental testing has shown that all the amplification products specified by these primers are of the predicted size and also hybridize with the appropriate cDNA or internal oligonucleotide probe" (Lowe, p. 1769, column 2, line 4-8).

4. Claims 4-7, 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harder et al. (J. Clin.Microbiol. (2001) Vol.39, No.12, pp.4413-4419), in view of Hemauer et al. (J. General Virology (1996) Vol.77, pp.1781-1785) and further in view of Lowe et al. (Nucleic Acids Res. (1990), Vol. 18, No.7, pp. 1757-1761).

Regarding claims 4-7, and 10, Harder discusses a method comprising: (a) providing a sample suspected to contain the target nucleic acid, (b) providing a pair of primers comprising a first and a second primer, (c) amplifying the target nucleic acid by

contacting the sample with the said pair of primers to produce an amplification product if the target nucleic acid is present in said sample, (d) contacting said sample with the pair of probes, wherein the members of said pair of probes hybridize to said amplification product within no more than five nucleotides of each other, wherein the first probe of said pair of probes is labeled with a donor fluorescent label and wherein the second probe of said pair of probes is labeled with a corresponding acceptor fluorescent label; and (e) detecting the presence or absence of fluorescence resonance energy transfer between said donor fluorescent label of said first probe and said acceptor fluorescent label of said second probe, wherein the presence of fluorescence resonance energy transfer is indicative of the presence of the target nucleic acid in the sample, and wherein the absence of fluorescence resonance energy transfer is indicative of the absence of the target nucleic acid in the sample (see p. 4414, "LC-depedent amplification of B19 DNA", lines 25-40, where Harder uses NS-1a and NS-1a' as primers and two adjacent donor/acceptor probes in a real-time FRET lightcycler PCR assay; and Figures 1 and 2).

Regarding claim 9, Harder discusses the method where amplification is performed using the FastStart SYBR green kit from Roche, which uses a FastStart Taq DNA polymerase that is a modified form of thermostable recombinant Taq DNA polymerase (Taq is a template-dependent DNA polymerase) (see p .4414, "LC-dependent amplification of B19 DNA").

Harder does not discuss the method whereby the first primer has a nucleic acid sequence consisting of SEQ ID NO: 15, and whereby the second primer has a nucleic

acid sequence consisting of SEQ ID NO: 17. Harder also does not discuss the method wherein the probe has a sequence consisting of SEQ ID NO: 11. However, Harder teaches primers and probes that are nearby to such sequences as the instant SEQ ID NO: 11, 15 and 17 that are located within the NS1 region of the Parvovirus B19 genome.

Hemauer teaches the Parvovirus B19 DNA, genome position 1924-2317, identified as Genbank Accession Number Z70553. This sequence comprises SEQ ID NO: 11 (nucleotides 147-172), SEQ ID NO: 15 (nucleotides 121-140) and SEQ I D NO: 17 (nucleotides 270-251). In Hemauer's research, he identifies this region (i.e. genome position 1924-2317) being within the NS1 coding region, and is more specifically included in the NS1-C region (see Figure 1). Hemauer also teaches nearby primers to amplify this region (see Table 2 on pg.1783).

One of ordinary skill in the art would have been motivated to modify the method of Harder to use primers of SEQ ID NO: 15 and 17 and a probe sequence of SEQ ID NO: 11 because Harder demonstrates the benefits of designing and using similar primers and probes targeting the NS1 region of the Parvovirus B19 genome, and Hemauer et al. shows that the Parvovirus B19 sequence comprising the primer sequences of SEQ ID NO: 15 and 17 and probe sequences of SEQ ID NO: 11 was known in the art and also designed nearby primers that amplify this same region. Additionally, Hemauer also notes that amplification of the NSC-1 region was able to show positive PCR results in contrast to other regions of the Parvovirus B19 genome

and also noted that there is a relatively conserved stretch of about 220 bp with only a few alterations in nucleotides 2020-2240 of this region (see pg.1783, right column). Therefore, since the sequences of primers SEQ ID NO: 15 and 17, and probe sequences of SEQ ID NO: 11 are located in this conserved stretch, one of skill would have recognized that amplification and detection of such a conserved region would allow for detection of multiple different parvovirus B19 sequences in a universal method. Therefore, the skilled artisan would have had a reasonable expectation of success in modifying the method of Harder to substitute for similar and equivalent primers and probes derived from the same well-known and amplifiable conserved stretch of the NSC-1 region, resulting in the predictable amplification and detection of multiple different parvovirus sequence variants. It would have been obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the claimed primer and probe sequences therein.

In the recent court decision *KSR International Co. v. Teleflex Inc., 82* 127 SCt 1727 (2007), the U.S. Supreme Court determined that if the combination of the claimed elements was "obvious to try" by a person of ordinary skill, this might show that such a combination was obvious under §103. Regarding "obvious to try", the Court stated:

"A person of ordinary skill is also a person of ordinary creativity, not an automaton. The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was "obvious to try." Id., at 289 (internal quotation marks omitted). When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103."

Since the claimed primers and probe simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for detection of the NS1 region of the Parvovirus B19 genome and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

With regard to the issue of equivalence of a polynucleotide sequence, MPEP 2144.06 notes "Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

With regard to the issue of reasonable expectation of success in using such equivalents at the time the invention was made, as shown in Lowe, one of skill in the art was clearly aware of the factors involved in designing amplification primers from a known sequence, and would have routinely and predictably designed any such primers. Specifically, Lowe teaches a computer program based on a set of rules which take into account both the sequence of the primers and the amplified region of DNA, such that primer-to-target hybridization is enhanced, while facilitating attainment of full-length extension products by minimizing non-specific product formation and self-priming (see

Abstract and p. 1757, column 2, line 33 to p. 1758, column 1, line 41). The program has been tested on a variety of gene products for RT-PCR, for both total and cytoplasmic RNA samples prepared by several different methods (Lowe, p. 1758, column 2, last 2 lines). "Experimental testing has shown that all the amplification products specified by these primers are of the predicted size and also hybridize with the appropriate cDNA or internal oligonucleotide probe" (Lowe, p. 1769, column 2, line 4-8).

5. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over either one of Schmidt et al. (2001), in view of Hemauer et al. (1996), and Lowe et al. (1990), as applied to claims 4, 5 and 8-10 above, OR Harder et al. (2001), in view of Hemauer et al. (1996), and Lowe et al. (1990), as applied to claims 4-7, 9 and 10 above and further in view of Andrus et al. (US 7,348,164).

The teachings of the primary references are discussed above. These references do not discuss the method wherein the primer and/ or the probe comprise a modified nucleotide or a non-nucleotide compound.

However, Andrus demonstrates that the use of modified nucleotides or non-nucleotide compounds in primers and probes which detect Parvovirus B19 sequences was conventional in the art at the time of the invention (see abstract, Figures, and col.9, lines 59-67). Therefore, one of skill in the art would have had a reasonable expectation of success in modifying the primer and/or probe of Schmidt, as modified by Hemauer and Lowe, or Harder, as modified by Hemauer and Lowe, to include a modified nucleotide or a non-nucleotide compound since Andrus demonstrates it was

conventional to do in the art at the time of the invention. It would have been *prima facie* obvious to one of skill in the art to carry out the claimed methods and use the claimed primers and/or probe comprising modified nucleotides or non-nucleotide compounds therein.

6. Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over either one of Schmidt et al. (2001), in view of Hemauer et al. (1996), and Lowe et al. (1990), as applied to claims 4, 5 and 8-10 above, OR Harder et al. (2001), in view of Hemauer et al. (1996), and Lowe et al. (1990), as applied to claims 4-7, 9 and 10 above, and further in view of Mosquera et al., "Simultaneous Detection of Measles Virus, Rubella Virus, and Parvovirus B19 by Using Multiplex PCR," J. Clin. Micro., 2002, Vol.40, No.1, pp.111-116.

The teachings of the primary references are discussed above. These references do not discuss the method wherein other target nucleic acids are detected in the same reaction.

However, it was conventional in the art to conduct multiplex PCR assays where Parvovirus B19 is detected within the multiplex, as demonstrated by Mosquera et al. Mosquera explains that it is beneficial to detect all three together as the rash illness caused by Rubella Virus, and Parvovirus B19 is easily confused with measles virus infection and differential diagnosis is recommended for surveillance activities (see abstract and pg.11, right column, first full paragraph). Therefore, one of skill in the art would have had a reasonable expectation of success in modifying the method of either

one of Schmidt, as modified by Hemauer and Lowe, or Harder, as modified by Hemauer and Lowe, to detect multiple target nucleic acids with Parvovirus B19 since Mosquera demonstrates that it was conventional in the art to conduct multiplex assays including Parvovirus B19 for the added benefit of being able to distinguish between viral infections which cause similar physical symptoms. It would have been *prima facie* obvious to one of skill in the art to carry out the claimed methods and also detect other target nucleic acids therein.

Response to Arguments

7. Applicant's arguments filed October 7, 2010 have been fully considered but they are not persuasive.

Applicant then argues that the 35 USC § 103(a) rejection of claims 4, 5 and 8-10 over Schmidt et al. (Vox Sanguinis, 2001, Vol.81, No.4, pp.228-235) in view of Hemauer (J. General Virology (1996) Vol.77, pp.1781-1785) and further in view of Lowe et al. (Nucleic Acids Res. (1990), Vol. 18, No.7, pp. 1757-1761) should be withdrawn since none of the cited references alone or in combination teach the specific sequences of SEQ ID NOS: 15, 17 and 11 or the combination of these sequences, as provided in the claims as amended. In addition, Applicant argues that there is no motivation for one of skill in the art to modify the teachings of Schmidt in view of Hemauer to achieve the specific combination of sequences as claimed and that Hemauer actually teaches away from designing primers in this region since other regions are more conserved. Furthermore, Applicant argues that selection of claimed primers was not "obvious to try"

by one of skill in the art and that based on the teachings of Lowe, there is no reasonable expectation of success for designing new primers. Applicant further argues that Hemauer teaches that the NS1-C region that comprises the claimed primers is only "relatively conserved" and actually choose primer sites outside of this region. Applicant further argues that Schmidt teaches the use of nested primers targeting the VP1/VP2 region and furthermore, that one of skill in the art would not be motivated to modify the assay of Schmidt since the "assay is highly reproducible" in its current form.

The Examiner asserts that while the prior art does not teach the use of primers or probes consisting of the sequences as cited in the amended claims, both Schmidt and Hemauer teach primers that were used in PCR amplification of the NS1 region of parvovirus B19 and therefore are useful for detection of this target sequence in a sample. In fact, Schmidt actually teaches primers and probes that overlap with the claimed primers or are within 23 bases of the claimed sequences, while Hemauer teaches primers that are about 200 bases away from the claimed sequences. Though Schmidt does not teach the NS1 target sequence itself, both Schmidt and Hemauer teach primers that can detect this sequence, and therefore it is obvious to combine the teachings of Schmidt for diagnostic detection of parvovirus B19 DNA in a sample with a teaching such as that of Hemauer that provides the NS1 sequence that can be used for primer and probe design. For purposes of motivation, there is no need to consider the specific primers taught by Hemauer, as Hemauer is used only to provide the target sequence. However, since Hemauer teaches a sequence analysis of parvovirus B19 to demonstrate the variability of isolates, the fact that certain regions are more conserved

than others, including the NS1 region, would provide motivation to one of skill in the art to try such regions, since relatively few (12) base changes were observed among 19 isolates in the 220-base region comprising the claimed sequences (Hemauer, p. 873, column 2, lines 6-11). With regard to the teachings of Schmidt, two PCR-based assays are presented. The first assay is based on the use of nested primers targeting the VP1/VP2 region and is designed for product analysis by gel electrophoresis, but was not cited by the Examiner (see Schmidt, p. 229, column 2, "Nested PCR"). However, it is the second assay that is most relevant to the instant claims since this is a real-time PCR assay that like the instant claims uses dual-labeled TaqMan probes for product detection and furthermore, uses primers that overlap or are within 23 bases of the claimed primers (see Schmidt, p. 229, column 2, "Quantitative TaqMan-PCR"). Finally, though Schmidt states that this assay is highly reproducible, reproducible quantification was only possible when the sample contained greater than 1000 copies of target sequence (Schmidt, p. 230, column 1, last three lines to first line of column 2). Therefore, one of skill in the art will recognize that additional optimization may be required for improving the sensitivity of the assay, which may require trying other primers.

Applicant then argues that, contrary to prior assertions by the Examiner, the claimed primers and probes do not represent structural homologs or "equivalents" derived from sequences suggested by the prior art. Applicant argues that primer and probe sequences taught by the prior art and the primer and probe sequences cited in the claims are not homologs since they do not share homology, despite the fact they

can hybridize to a common sequence, particularly when they target sequences tens or hundreds of bases apart. The Examiner clarifies that the use of "structural homologs" was not intended to compare different primer sequences that bind to a common target sequence but rather that equivalency has been recognized in the prior art since the cited primers and probes of SEQ ID NOs. 11, 15 and 17 are homologous to sequences taught by Hemauer and therefore are structural homologs derived from the prior art sequence. Since one of ordinary skill in the art would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are prima facie obvious over the cited reference of Hemauer in the absence of secondary considerations.

Applicant further argues in view of the cited prior art that the present invention was not "obvious to try", particularly since none of the cited prior art provides direction as to which of the many possible choices of oligonucleotides found within the >2kb long NS gene region is likely to be successful when used in an amplification-based assay as claimed. Applicant argues that it was not obvious to one of skill in the art to select SEQ ID NOs. 15, 17 and 11 from the broad range and large number of possible oligonucleotides and combinations from the parvovirus genome, particularly without specific direction from the prior art. The Examiner asserts that, as discussed above, Schmidt teaches a real-time PCR amplification assay that uses primers that either overlap or are within 23 bases of the claimed oligonucleotides targeted to the 2030-2171 bp region of the NS1 gene region. Thus, Schmidt has provided a relatively narrow region in which one of skill in the art would attempt to design primers and probes for

improved detection of parvovirus B19, using the primer design software available at the time of the invention. In addition, Hemauer teaches the sequence of this region and provides further motivation to target the region since the reference indicates that the region is relatively conserved.

Finally, Applicant further argues that the teachings of Lowe in which the success of PCR reactions is based on amplification products of the predicted size and which hybridize with an appropriate probe does not provide a reasonable expectation of success for primers used in a complex detection assay for amplification of a virus with highly variable sequences. Applicant argues that Lowe does not teach or suggest the use of important primer design criteria, including the Tm range as well as primer sequence based on known variants of the target site and limiting false priming sites. The Examiner asserts that Lowe provides a software program for guidance for designing appropriate primers for a given target sequence based on a number of factors, including suggested primer length and GC content and the Tm of the amplified product (Lowe, p. 1757, column 2, second to last line to p. 1758, column 1, line 41). In addition, Lowe discloses that the program is "focused on guaranteeing the uniqueness of primer-target hybridization by avoiding obvious problems such as long runs of individual bases and regions of self-complementarity" (Lowe, p. 1760, column 2, line 11 to p. 1761, column 1, line 2). Thus, one of skill in the art is provided general guidance in primer design by Lowe, but would also have available the primer and probe design methods available at the time for quantitative TaqMan PCR assays using dual-labeled probes (see Schmidt, p. 229, section on Quantitative TaqMan-PCR and use of SDS-

software). Based on the available primer design methods at the time of the invention and knowledge of the sequence of the 2030-2171 bp region of the NS1 gene that is known to be relatively conserved, as provided by Hemauer, one of skill in the art will have a reasonable expectation of success in amplification of this region using equivalents of the claimed primers.

Therefore, based on all the discussions above, the 103(a) rejection of claims 4, 5 and 8-10 over Schmidt in view of Hemauer and further in view of Lowe is maintained. Note, that the rejection of claims 4-7, 9 and 10 over Harder in view of Hemauer and further in view of Lowe is also maintained since Applicant provided no arguments against this rejection. Similarly, the rejection of dependent claims 15 and 16 are maintained since limitations taught by Andrus and Mosquera are not argued separately.

Summary

8. Claims 4-10, 15 and 16 are rejected. No claims are allowable.

Conclusion

9. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David C. Thomas whose telephone number is 571-272-3320 and whose fax number is 571-273-3320. The examiner can normally be reached on 5 days, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David C Thomas/
Examiner, Art Unit 1637

/Kenneth R Horlick/
Primary Examiner, Art Unit 1637